REMARKS

Status of the Claims and Amendment

Claim 15 has been amended editorially to include a space between "data" and "from". Claims 1-21 are all the claims pending in this application. Claims 10 and 12 are withdrawn from consideration as being drawn to a non-elected invention. Claims 1-9, 11 and 13-21 are rejected. No new matter is added.

Information Disclosure Statement

Applicants thank the Examiner for consideration of the Information Disclosure Statement filed March 23, 2010, by returning a signed and initialed copy of the PTO Form SB/08 submitted therewith.

Response to Claim Objections

Claim 15 is objected to because the word "datafrom" should be amended to separate the words "data" and "from."

In response, claim 15 has been amended as suggested. Withdrawal of the grounds of objection is respectfully requested.

Withdrawn Rejection

Applicants thank the Examiner for withdrawing claims rejections under 35 U.S.C. § 112, 2nd paragraph in view of the claim amendments.

Request for Rejoinder of Dependent Method Claim 10

Applicants note that claim 10 includes all the limitations of the allowable method claim 1 (from which claim 10 indirectly depends), and is believed to be in condition for rejoinder with claims 1-9, 11, and 13-21.

Accordingly, rejoinder of dependent method claim 10 is respectfully requested.

Claims 1-9, 11, and 13-21 Are Not Rendered Obvious Over The CDR Handbook, Berry, Holford, Veyrat-Follet, and Rooney

Claims 1-9, 11, and 13-21 are rejected under 35 U.S.C. 103(a) as being allegeldy unpatentable over the CDER Handbook (from Department of Health and Human Services, FDA. http://www.fda.gov/cder/handbook/The CDER Handbook), in view of Berry (*BioPharmaceutical Report* 9(2): 1-11 (2001)) and in further view of view of Holford *et al.* (*Ann. Rev. Pharmacol. Toxicol.*40: 209-234 (2000)) and Veyrat-Follet *et al.* (*Clin. Phamacol. Ther.* 68: 677-687 (2000)), in further view of Rooney *et al.* (*DDT*, 2001, 6(5): 802-806).

The Examiner asserts that Applicants' arguments are moot in view of this new ground of rejection.

The CDER handbook, Berry, Holford, and Veyrat-Follet documents are asserted for the same reasons set forth in the previous Office Action mailed November 23, 2009. For brevity, these reasons are not reiterated herein.

The Examiner admits that the CDR Handbook and Berry do not teach a computer model for clinical trial design, and that neither the CDER Handbook, Berry, nor Holford combined with Veyrat-Follet specifically teach an *in silico* patient or computer model that interacts, as claimed.

In this respect, Rooney is asserted for allegedly teaching the use of computer-assisted trial designs (CATD) for rational decision making with respect to go/no-go decisions, clinical trial design, dose and end-point selection and the positioning of a product in the market place based on its commercial advantages. The Examiner asserts that the CATD uses mathematical models of drug action and disease state and progression to be inputted into computer software that simulate the clinical trial process.

Thus, the Examiner concludes that it would have been *prima facie* obvious, and one of ordinary skill in the art would have been motivated to implement the pre-clinical to Phase IV clinical trials outlined by the FDA in the CDER handbook for newly tested drugs, with the model algorithms of Berry that may be adjusted according to data obtained from the trials, and to include computer simulation for each step of the trial design as taught by Holford and by Veyrat-Follet to provide a streamlined and efficient drug design. In addition, the Examiner asserts that Rooney would have motivated one of ordinary skill in the art to use the computer to simulate the entire design process using CATD mathematical models that provide interactive feedback.

Applicants respectfully disagree, and note that the Examiner has failed to establish a *prima facie* case of obviousness for at least the following reasons.

As admitted by the Examiner, neither the CDER Handbook, Berry, nor Holford combined with Veyrat-Follet teach or suggest all the claim limitations, i.e., an *in silico* patient or computer model that interacts, as claimed. M.P.E.P. § 2143. Specifically, none of these cited documents teach or suggest the presently claimed method of performing interactive clinical trials in which a computer model or *in silico* patient is created, or adjusting the computer model or *in silico* patient and computer simulations based on the results of the clinical trial.

As Applicants have previously argued, the Examiner's rationale with regard to the teachings in each of the CDER Handbook, Berry, Holford and Veyrat-Follet is premised upon an inaccurate understanding of these references, and this rationale is repeated once more in the present Office Action.

For instance, even though Applicants' claimed method complies with the FDA's guidelines in the CDR Handbook, the CDR Handbook does not render Applicants' presently claimed method obvious because the CDR Handbook merely describes the drug development process from pre-clinical to NDA (New Drug Application) review, and is the FDA's guideline for meeting the statutory requirements for compliance with regard to drug efficacy and safety (from pharmacology and toxicology data) for each stage of the drug development process. Also, Berry is a review of statistical methods used for the design and during execution of clinical trials. In this regard, the model disclosed by Berry describes a statistically-based model from the family of "Adaptive Trial Design", where clinical results obtained in clinical trials are analyzed statistically ("top-down"). In contrast, the present invention provides a mathematical model, where a mechanistic model based on understanding of the underlying process is employed ("bottom-up"). This distinction has been described in the disclosure of the present as-filed specification, and has been acknowledged by the Examiner in the previous Office Action mailed November 23, 2009 (see page 7, 2nd paragraph). That is, an important difference is that the Bayesian statistical method of Berry does not include a mathematical model or an *in silico* patient.

The deficiencies of Holford and Veyrat-Follet have been previously presented in the Amendment filed March 23, 2010, and are applicable to this rejection for the same reasons.

Rooney does not cure the deficiencies of the CDER Handbook, Berry, Holford and Veyrat-Follet. Although Rooney teaches CATD, Rooney does not teach or suggest the interaction between an *in silico* patient or computer model and the clinical trial, as claimed. Specifically, Rooney merely states that "[t]he CATD uses mathematical models of drug action and disease state and progression to be inputted into computer software that can simulate the clinical trial process. The technique uses knowledge-based quantitative analysis (page 803, column 1)" (see Office Action page 6, 3rd paragraph citing to page 802, column of Rooney). However, this is merely a "sales pitch", and Rooney provides no further teaching or guidance as to how to successfully achieve the claimed invention or even successfully implement CATD for that matter. In this respect, Rooney does not show or provide examples to show how CATD is successfully implemented. That is, Rooney does not teach or suggest a mathematical model for disease progression that would enable one of ordinary skill in the art to make or practice the claimed invention. Rather, the CATD, as disclosed in Rooney, provides just the headlines as to what may be done without a reasonable expectation that one of ordinary skill in the art may even successfully implement CATD. As explicitly disclosed at page 806, 2nd column of Rooney, the authors themselves recognized and list the "barriers [which] exist [to] have the potential to limit [the CATD's] successful implementation."

In this respect, Applicants note that "in order to render an invention unpatentable for obviousness, the prior art must enable a person of ordinary skill to make and use the invention." *In re Kumar*, 418 F.3d 1361, 1368 (Fed. Cir. 2005) (citing from Beckman Instruments, Inc. v. LKB Produkter AB, 892 F.2d 1547, 1551 (Fed. Cir. 1989)). The Federal Circuit has found that an obviousness finding was appropriate only where the prior art "contained detailed enabling methodology for practicing the claimed invention, a suggestion to modify the prior art to practice

the claimed invention, and evidence suggesting that it would be successful [emphasis added]." *In re O'Farrell*, 835 F.2d 894, 902 (Fed. Cir. 1988). As discussed above, because neither the CDER Handbook, Berry, Holford, Veyrat-Follet, and Rooney, separately or combined, teach or suggest the presently claimed method of performing interactive clinical trials in which a computer model or *in silico* patient is created, or adjusting the computer model or *in silico* patient and computer simulations based on the results of the clinical trial, one of ordinary skill in the art would not have been enabled to obtain or use the presently claimed invention.

In summary, the claimed invention is not rendered obvious over the CDER Handbook, Berry, Holford, Veyrat-Follet, and Rooney, because the cited references do not teach or suggest all the claim limitations, nor enable one of ordinary skill in the art to successfully perform the interactive use of an *in silico* patient and actual data from clinical trials, as in the claimed invention.

Reconsideration and withdrawal of the rejection under 35 U.S.C. § 103(a), is respectfully requested.

Conclusion

In view of the above, reconsideration and allowance of this application are now believed to be in order, and such actions are hereby solicited. If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

The USPTO is directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

Respectfully submitted,

/Tu A. Phan/

Tu A. Phan, Ph.D.
Registration No. 59,392

SUGHRUE MION, PLLC
Telephone: (202) 293-7060
Facsimile: (202) 293-7860

WASHINGTON OFFICE
23373
CUSTOMER NUMBER

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